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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/644,498	08/23/2000	Tuija Helina Salin-Nordstrom	2508.13US01	1667

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EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	9

DATE MAILED: 09/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/644,498	SALIN-NORDSTROM, TUIJA HELINA	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *15,16,23,25-31,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 17-22, 24, 32-33, 36-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-59* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2-5,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (Claims 1-59) in part drawn to an *in vitro* method of culturing cells in Paper No. Paper No. 7 (25 July 2002) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 15, 16, 23, 25-31, 34, and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 1-14, 17-22, 24, 32-33, and 36-59 will be examined to the extent that they read on methods of administering FGF-2 (also known as bFGF or basic fibroblast growth factor).

Status of Application, Amendments, and/or Claims

2. The Response to Election Requirement of 25 July 2002 (Paper No. 7) has been entered in full. Claims 60-63 are canceled. Claims 15, 16, 23, 25-31, 34, and 35 are withdrawn from consideration, as discussed above. Claims 1-14, 17-22, 24, 32-33, and 36-59 are under examination.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Specification

4. The specification is objected to because of the following informalities: "neuroaxis" is misspelled as "neuraxis' (pp. 1). Appropriate correction is required.

5. The specification is objected to because of the following informalities: "poly-L-lysine" is misspelled as "poly L-lysine". (pp. 15). Appropriate correction is required.

6. The specification is objected to because of the following informalities: "MAP2ab" should read "MAP2". (pp. 16). Appropriate correction is required.

Claim Objections

7. Claims 1-3, 6-10, 12-14, 17-22, 32, 36, 39-45, 47-52, 54, and 57 are objected to because of the following informalities: the Claims recite a non-elected species. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-14, 17-22, 24, 32-33, and 36-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. Claims 1-11 are directed to an *in vitro* method of *in vitro* production of neurons from astrocytes comprising culturing and exposure to bFGF. Claims 12-14, 17-22, 24, and 32-33 are

directed to an *in vitro* method of producing a second cell type from astrocytes comprising culturing and subsequent treatment with bFGF to yield oligodendrocytes, neurons, or multipotent cell types. Claims 36-37 are directed to an *in vitro* method of treating astrocytes to product a population of multipotent cells comprising culturing and subsequent treatment with bFGF. Claim 38 is directed to an *in vitro* method of treating astrocytes to produce a population of cells that includes neurons and/or oligodendrocytes comprising a step of culturing the astrocytes and a subsequent step of treating with bFGF. Claims 39-48 are directed to an *in vitro* method of manipulating glial cells to produce multipotent cells comprising pre-treatment, dissociation, and treatment with bFGF. Claims 49-56 are directed to a method of screening growth factors for transdifferentiation comprising culturing astrocytes, dissociation, plating in test well means, treating with a test growth factor and comparing that to control test well means treated with bFGF to see if the test growth factor yields oligodendrocytes and/or neurons. Claims 57-59 are directed to an *in vitro* method for producing neurons from astrocytes comprising culturing astrocytes and subsequent treatment with bFGF.

10. The specification asserts that neural stem cells can be isolated; cultured to form astrocytes, and that these astrocytes can be caused to turn into a number of other neural cells by treatment with bFGF. Example 6.1.1 speaks to isolation of human neural stem cells, but does not give any experimental detail as to how these stem cells were isolated. One skilled in this art would be unable to repeat the experiment in the absence of these details. In Example, 6.1.2, more experimental details are provided as to how to isolate neural stem cells from an animal, but the example is silent with respect to the animal from which the cells are isolated.

11. The art teaches that most adult mammalian brains contain stem cells but does not teach how to isolate such stem cells from all animals. In addition, the art teaches that radial astrocytes, present during development, and subventricular zone astrocytes, present through adulthood, can be induced to differentiate into glial and neuronal cells via treatment with growth factors such as but not limited to epidermal growth factor (EGF) (Rao, 1999).

12. However, the art notes that most experiments are performed on murine cells and using primary neural cultures. For example, Weiss et al. (USPN 5,750,376) teaches the use of mouse primary neural cultures to generate three types of cultures, neurons, astrocytes or oligodendrocytes (Col 8 37-56). Weiss et al. also teaches a method for the *in vitro* proliferation and differentiation of neural stem cells and stem cell progeny comprising the steps of (a) isolating the cell from a mammal, (b) exposing the cell to a culture medium containing a growth factor, such as basic fibroblast growth factor (bFGF or FGF-2) (c) inducing the cell to proliferate, and (d) inducing the cell to differentiate (Col. 10 56-67; Col. 11 1-11; Col. 16 58-67). Weiss et al. describes the method as yielding neurons detected with MAP-2, astrocytes detected with GFAP, and oligodendrocytes detecting with O4 (FIG. 3A-D). Weiss et al. teaches a method wherein the cells are treated for 3-4 days with the growth factor and then it is removed for 4-5 days. In addition, the cells are maintained for 3-10 days *in vitro*, more particularly about after 6-7 days *in vitro* the proliferating neurospheres are fed every 2-7 days preferably every 2-4 days by gentle centrifugation and resuspension in complete medium containing a growth factor such as bFGF (Col. 17 37-67). Weiss et al. also teaches a method using neural progenitor cells as a method screening possible unknown growth factors including using bFGF as a control among other (Col. 19-22).

13. Thus the claimed invention is directed to an *in vitro* system for transdifferentiation of astrocytes into neurons, oligodendrocytes, and multipotent cells is not supported by the teachings of the prior art. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Specific biological actions/activities that bFGF would effect; Which astrocytes are to be used in the experiment?; Expectation that the neurons, oligodendrocytes, or multipotent cells would be functional; Survival time of transdifferentated cells. In addition, most references included in the Information Disclosures use mice and it is not acknowledged in the art that success in mice is predictive of humans. The specification does not provide guidance on how to overcome expected obstacles for one of ordinary skill in the art at the time the application was filed to be guided by the specification and prior art with a reasonable expectation of successfully repeating the experiments. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

14. Due to the large quantity of experimentation necessary to force astrocytes (non-fetal or non-SVZ) to differentiate into neuronal cells, the lack of direction/guidance presented in the specification regarding evaluating FGF-2 effects on said astrocytes, the absence of working examples directed to said astrocytes that have become neuronal via treatment with FGF-2, the complex nature of the invention, the unpredictability of the effects of a growth factor on all astrocytes (Rao, 1999), and the breadth of the claims which fail to recite limitations of what type of neuron or multipotent cells would result from bFGF treatment, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Regarding glial cells, the art recognizes that glial cells cover a large variety of cells including astrocytes including fibrous, protoplasmic, radial, and SVZ, microglia, Schwann cells, oligodendrocytes, and including glial cell lines (Nolte, The Human Brain: An Introduction to Its Functional Anatomy). Due to the large quantity of experimentation necessary test all the subtypes of glial cells, the lack of direction/guidance presented in the specification regarding evaluating FGF-2 effects on all subtypes of glial cells, the absence of working examples directed to glial cells (non-fetal) that have become neuronal via treatment with FGF-2, the complex nature of the invention, the unpredictability of the effects of a growth factor on glial cells and the breadth of the claims which fail to recite limitations of what type of neuron or multipotent cells would result from bFGF treatment, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

16. Regarding neurons, the art recognizes that neurons covers a huge variety of cells. Neurons are present in both central nervous system and peripheral and within each branch excitatory and inhibitory, then the various subtypes based upon location with the nervous system and the type of neurotransmitters and neuromodulators expressed or responded to by said neurons and various neuronal cell lines (Kandel et al., Principles of Neural Science). Due to the large quantity of experimentation necessary to identify distinguishing characteristics of each neuron subtype, the lack of direction/guidance presented in the specification regarding neuronal markers of specific subtypes (e.g. GAD, TH, ChAT, DDC, DBH), the absence of working examples directed to neuronal characteristics (neurotransmitter and/or neuromodulators production and/or release), the complex nature of the invention, the unpredictability of what type of neurons will be derived from differentiation of progenitors in culture (USPN 5,750,376 Col.

18-20), and the breadth of the claims which fail to recite limitations of which neuronal cells are considered neurons, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

17. Regarding multipotent cell type, the art recognizes two major classes of multipotent stem cells in the central nervous system (CNS), epidermal growth factor (ECF)-dependent neurosphere cells and FGF-dependent stem cells, both can give rise to neurons, astrocytes, and oligodendrocytes. Each type, neurons, astrocytes, and oligodendrocytes contain numerous subtypes within each as discussed above. In addition, astrocyte restricted precursors (APC), glial restricted precursors (GRP), and neuronal restricted precursors, each limited to differentiating into its type of cell (Lee et al. 2000). Also, radial and SVZ astrocytes can be multipotent (Doetsch et al., 1999). Due to the large quantity of experimentation necessary to identify which multipotent cells and what types and subtypes of descendent cells may be formed, the lack of direction/guidance presented in the specification regarding evaluating the viability of derived multipotent cells, the absence of working examples directed to the multitude of multipotent cell types that have yielded astrocytes, neurons, and/or oligodendrocytes via treatment with FGF-2, the complex nature of the invention, the unpredictability differentiating multipotent cells in culture (Rao et al., 1998; Rao, 1999), and the breadth of the claims which fail to recite limitations of what type of neuron or multipotent cells would result from bFGF treatment, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Summary

18. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
September 13, 2002

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER